## REMARKS

Claims 1, 3-20, and 22-32 and 38-40 are pending.

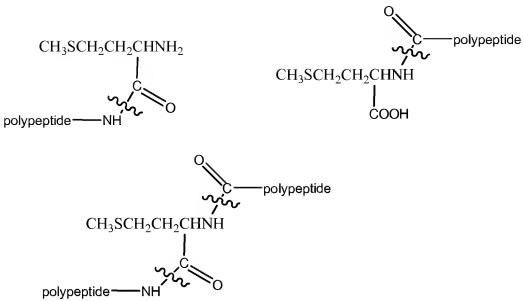
**35 U.S.C. § 102 Rejection**

Reconsideration is respectfully requested of the rejection of claims 1, 7-9, 20, and 23-25 as anticipated by U.S. Patent No. 4,961,926 (Gabrilove) under 35 U.S.C. § 102(b). Claim 1 is directed to a method for reducing oral mucositis in a human or animal patient exposed to radiation. The method comprises administering to the patient an effective amount of a protective agent comprising methionine having the structure

or a pharmaceutically acceptable salt thereof. Claim 20 is similar to claim 1 but differs in that the patient is undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. The Office states that the interpretation of the phrase of claim 1 of "administering a protective agent comprising [methionine]" can include other agents in addition to methionine.[1]

Gabrilove discloses methods of preventing mucositis comprising administering granulocyte colony stimulating factor (GCSF) or a polypeptide analog thereof. In particular, the GCSF analog may be a nonglycosylated polypeptide having an amino acid sequence identical to the sequence of the polypeptide component of naturally occurring GCSF (GCSF contains at least 144 amino acids) except for the presence of an additional methionine at the N-terminus. In one embodiment described in the Gabrilove reference, this 20,000 Dalton protein has one additional methionine residue to give a total of 145 amino acids. In contrast, methionine is small molecule of approximately 150 Daltons. Further, the methionine attached to the GCSF polypeptide would have one of the following structures depending on whether it is the N-terminus, C-terminus or incorporated in the middle of the protein.

[1] See Office action dated June 27, 2008 at page 3.




For a polypeptide structure comprising a methionine unit to fit into the structure of claim 1 or 20, the remainder of the polypeptide structure would have to be a pharmaceutically acceptable salt. A salt is defined as "any of a class of compounds formed by the replacement of one or more hydrogen atoms of an acid with elements or groups, which are composed of anions and cations, and which usually ionize in solution."[2] The formation of a polypeptide is a reaction where water is lost and a covalent amide bond is formed between an amine group of one amino acid and a carboxylic acid group of another amino acid. When water is lost, the -OH group of the carboxylic acid and a proton of the amine is lost. Thus, the .resulting polypeptide comprises one or more of the structures depicted above in which the methionine moiety is covalently bonded to the remainder of the peptide structure. This product does not meet the definition of a salt and the structure of claim 1 and 20 are not found upon incorporation of a methionine into a polypeptide. Thus, Gabrilove does not anticipate claims 1, 7-9, 20, and 23-25 under 35 U.S.C. § 102(b).

[2] See *Dictionary.com Unabridged (v 1.1)*. Random House, Inc. http://dictionary.reference.com/browse/SALT (accessed: September 23, 2008).

**35 U.S.C. § 103 Rejection**

Reconsideration is respectfully requested of the rejection of claims 3-19, 22, and 26-32 as unpatentable over U.S. Patent No. 6,265,386 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a). Claims 3-19 depend on claim 1 and incorporate all the elements of claim 1. Claims 22 and 26-32 depend on claim 20. Claims 1 and 20 are described in detail in connection with the § 102 rejection. The Office admits that the Campbell reference fails to teach reducing mucositis but asserts that it "would have been obvious to one of ordinary skill in the art to ... substitute the compound of Gabrilove and administer D-methionine..." because Kil et al. teach administering methionine to ameliorate neurotoxicity.[3]

As the Office further admits, the Campbell patent makes no mention of mucositis resulting from any type of insult; and that the patent provides no reason why methionine or methionine-like moieties would have any value in dealing with mucositis resulting from radiation exposure or administration of an anti-tumor platinum-coordination compound.

Moreover, there is no reason provided why a skilled person would have substituted methionine as disclosed by Kil for the GCSF protein of Gabrilove to treat mucositis resulting from radiation exposure or administration of an anti-tumor platinum-coordination compound. A skilled person would have attributed the anti-mucositis effect of the GCSF protein to the specific structural aspects of the protein and not solely or primarily to the presence of an additional methionine residue at the N-terminus. From the Gabrilove disclosure, a skilled person would have learned that recombinant hG-SCF (rhG-CSF) is "a specific growth and differentiation factor for neutrophil granulocytes"[4] and that "recombinant hG-SCF may reduce the incidence of mucositis by enhancing the number of neutrophils, as well as their functional capability to guard the mucosal barriers more efficiently"[5]. From these statements, a skilled person would have known that the primary, secondary, and tertiary structure of the 20,000 Dalton rhG-CSF protein

[3] See Office action dated June 27, 2008 at page 5.
[4] See U.S. Patent No. 4,961,926, column 2, lines 41 to 43.
[5] See U.S. Patent No. 4,961,926, column 7, line 67 to column 8, line 14.

was instrumental in its neutrophil granulocyte growth stimulation and mucositis protection functions.

A skilled person would not have expected monomeric methionine, a 150 Dalton small molecule, to provide the same physiological effect as the 20,000 Dalton GSCF protein, regardless of whether an additional methionine unit happens to be present at the N-terminus of the protein. Even if it were assumed that an additional methionine at the N-terminus of the GSCF protein is somehow instrumental in imparting significant properties to the protein as a whole, one skilled in the art would scarcely expect that the monomeric amino acid by itself would provide a comparable effect. By way of example, proteins, including GSCF proteins act upon cell components through various chemical and physical interactions. In particular, the primary, secondary, and tertiary (e.g., three dimensional) structure of the protein including surfaces for binding and interacting with various molecules is well known to be essential to the biological function which the protein exhibits. A protein can also undergo various conformational changes upon binding a molecule at a particular binding site. Monomeric methionine does not have the same type of complex three-dimensional structure, and would not be expected to stimulate growth of neutrolphil granulocytes. Thus, a person of ordinary skill would not have expected methionine by itself to be an effective agent against mucositis based on the Gabrilove disclosure alone or as combined with the Campbell disclosure.

Kil et al. does not remedy the deficiencies of Campbell or Gabrilove. Kil et al. teach combinations of chemoprotectants that ameliorate at least one side effect of chemotherapy. However, like the Campbell patent, Kil et al. makes no mention of mucositis resulting from any type of insult; and provides no reason why methionine or methionine-like moieties would have any value in dealing with mucositis resulting from radiation exposure or administration of an anti-tumor platinum-coordination compound. As described above for the combination of the Campbell patent and Gabrilove, the combination of Campbell, Gabrilove, and Kil would not have provided a reason to combine the teachings of the references and even if the teachings were combined, the combination would not have led a person of ordinary skill to find the present claims for reducing mucositis using the small molecule methionine obvious for at least the same

reasons as described above for the Campbell and Gabrilove combination. Further, as described for the Campbell and Gabrilove combination, a person of ordinary skill would not have expected methionine by itself to be an effective agent against mucositis based on the combination of Campbell, Gabrilove, and Kil disclosures.

The Office further asserts that administration of methionine for gastrointestinal toxicity would have reduced oral mucositis because gastrointestinal toxicity is closely related to oral mucositis.[6] However, radiation treatment is usually targeted to a specific area of the body wherein the diseased tissue is located. Thus, different side effects arise depending on the location of the diseased tissue. For example, mucositis may develop in patients receiving radiation treatment wherein mucosal tissue is in the field of the radiation exposure. In particular, oral mucositis commonly develops in treatment of cancers in the oral cavity or nasopharyngeal area due to the proximity of the oral mucosa to the tissues targeted by radiation treatment. In contrast, when the diseased tissue targeted for radiation treatment is not in proximity to mucosal tissue, mucositis will not inevitably arise from the radiation treatment. By way of example, radiation treatment of a breast tumor or tissue proximate to a surgically removed breast tumor does not necessarily result in mucositis because mucosal tissue is not in close proximity to the diseased breast tissue. Of course, radiation may cause problems other than mucositis in the tissue targeted. In fact it usually does; but these effects have no relevance to the method herein claimed. Examples of side effects arising from damage to healthy tissue, other than mucosal tissue, that is in the field of radiation exposure are appetite loss from radiation damage to brain cells, gastrointestinal disorders from radiation damage to cells in the gastrointestinal tract and/or abdomen, and neurotoxicity from damage to nerve cells. This pattern of toxicities shows that the mechanisms of damage from radiation exposure are different in different tissues and depending on the specific region of exposure to radiation, different side effects arise. Further, because the mechanisms of radiation damage to different tissues is unpredictable, a skilled person would not have had a reasonable expectation that administration of methionine would have been beneficial to ameliorate oral mucositis resulting from radiation exposure.

[6] See Office action dated June 27, 2008 at page 6.

Further, while oral mucositis may be an effect of chemotherapy, mucositis resulting from treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound occurs in fewer patients than other side effects such as, for example, ototoxicity, neurotoxicity, weight loss, and alopecia. Specifically, the cisplatin dosages exemplified in the Campbell patent and Kil reference would not inevitably have resulted in mucositis. Thus, a patient receiving treatment with an anti-tumor platinum-coordination compound could develop ototoxicity, neurotoxicity, weight loss, and alopecia, and not inevitably develop oral mucositis. This pattern of side effects shows the variations in mechanism of damage to cells in different tissues. Since there is no basis for one skilled in the art to know that mucositis was actually suffered by any subject exposed to cisplatin as described by Campbell or Kil, there is no basis for one skilled in the art to infer that any subject suffering from mucositis was ever treated with methionine according to either the Campbell or Kil experimental protocols. Much less is there anything in these references that would lead one skilled in the art to believe that methionine treatment might have been effective to control mucositis, or that it ever could be. Thus, the unpredictability of the side effects, combined with absence of any teaching that methionine might be effective against mucositis from any source, would have foreclosed any reasonable expectation that methionine would have been effective to ameliorate oral mucositis resulting from administration of an anti-tumor platinum-coordination compound.

Reconsideration is respectfully requested of the rejection of claims 38-40 as unpatentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a). Claim 38 is directed to a method of treating mucositis wherein the patient is exposed to radiation and is undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. As described in more detail above, Campbell and Kil disclose use of methionine to protect from various side effects of chemotherapy, but do not discuss or even mention mucositis as a side effect. Gabrilove discloses methods of treating mucositis with a 20,000 Dalton polypeptide. None of the cited references provide a reason why a 150 Dalton monomeric methionine would have been substituted for the polypeptide. Further, even if such a substitution would have been made, a person of skill in the art would not have had a reasonable expectation

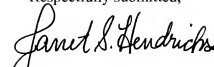
that methionine would have been successful to treat mucositis from a reading of the cited references. As discussed above, the three-dimensional structure of the GSCF protein is disclosed to be the reason for activity against mucositis. Thus, claims 38-40 are patentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a).

It is respectfully submitted that the Office has failed to establish obviousness based on the cited references or by evidence of the level of skill in the art or the nature of the problem that is not based upon impermissible hindsight reconstruction. Thus, claims 3-19, 22, 26-32 and 38-40 are patentable over the cited references.

## CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

Respectfully submitted,



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